600-111

#10

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,529,593

Attn: Box Patent Ext.

Inventors: Raymond P. Warrell, Jr.
and Richard S. Bockman

Assignee: Sloan-Kettering Institute
for Cancer Research

SUBMISSION OF APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Honorable Commissioner of Patents and
Trademarks
Washington, D.C. 20231

Sir:

Submitted herewith are the following papers in support of an application for extension of patent term pursuant to Patent Term Restoration Act of 1984, 35 U.S.C. § 156, with respect to the subject patent, filed on behalf of Sloan-Kettering Institute for Cancer Research, assignee of U.S. Patent No. 4,529,593, a corporation organized under the laws of the State of New York, located in New York, New York.

(1) Application for Extension of Patent Term Under 35 U.S.C. § 156 including:

EXHIBIT 1 - Package Insert describing the approved product;
EXHIBIT 2 - Copy of the FDA letter announcing approval of gallium nitrate;
EXHIBIT 3 - Copy of the subject patent;
EXHIBIT 4 - Copy of Certificate of Correction;
EXHIBIT 5 - Copy of Maintenance Fee Statement and receipt of Maintenance Fee payment; and
EXHIBIT 6 - Chronology of major events respecting the approved product.

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120 BC 03/21/91 4529593 2 111 540.00 CK

In re: U.S. Patent No. 4,529,593

(2) A check in the amount of $ $600.00 to cover the fee for the extension of patent term.

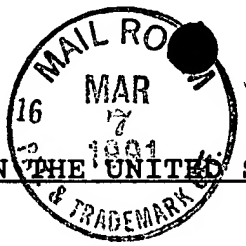
The undersigned hereby verifies that the copy of the application for Request For Patent Term Extension Under 35 U.S.C. § 156 of U.S. Patent No. 4,529,593 submitted herewith is a true and correct copy of the original of said application.

Respectfully submitted,

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH

Dated: March 7, 1991 By: _____

John P. White, Esq.
Registration No. 28,678
Cooper & Dunham
30 Rockefeller Plaza
New York, New York 10112
(212) 977-9550
Attorney for Assignee



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,529,593

Attn: Box Patent Ext.

Inventors: Raymond P. Warrell, Jr.
and Richard S. Bockman

Assignee: Sloan-Kettering Institute
for Cancer Research

REQUEST FOR EXTENSION OF PATENT
TERM UNDER 35 U.S.C. § 156

Honorable Commissioner of Patents and
Trademarks
Washington, D.C. 20231

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156, Sloan-Kettering Institute for Cancer Research, assignee of U.S. Patent No. 4,529,593 by an assignment from the inventors recorded on June 20, 1984 at Reel 4278, Frame 304, hereby requests an extension of the patent term for said patent. Sloan-Kettering Institute for Cancer Research is a unit of Memorial Sloan-Kettering Cancer Center (MSKCC).

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740 and follows the numerical format and headings set forth in 37 C.F.R. § 1.740:

1. A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

The approved product is gallium nitrate (GANITE™), the package insert for which is attached as Exhibit 1. Gallium nitrate injection is a clear, colorless, odorless, sterile solution of gallium nitrate, a hydrated nitrate salt of the group IIIa element, gallium. Gallium nitrate is formed by the reaction of elemental gallium with nitric acid, followed by crystallization of the drug from the solution. The stable, nonahydrate, $[Ga(NO_3)_3.9(H_2O)]$ is a white, slightly hygroscopic, crystalline powder of molecular weight 417.87, that is readily soluble in water. Each milliliter of gallium nitrate injection contains gallium nitrate 25 mg (on an anhydrous basis) and sodium citrate dihydrate 28.75 mg. The solution may contain sodium hydroxide for pH adjustment to 6.0-7.0.

2. A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review occurred under Section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 355. Section 505 provides for the submission and approval of new drug applications (NDAs).

3. An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

Gallium nitrate was approved by the Food and Drug Administration (FDA) for commercial marketing pursuant to Section 505 of the FFDCA on January 17, 1991. A copy of the letter from FDA announcing that approval is attached as Exhibit 2.

4. An identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the FFDCA, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) and the provision of law under which it was approved.

The only active ingredient in the approved product is gallium nitrate. Gallium nitrate has not been previously approved for commercial marketing or use under the FFDCA.

5. A statement that the application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved for commercial marketing on January 17, 1991, and the last day within the sixty-day period permitted for submission of an application for extension of a patent is March 18, 1991. The date of submission of the present application is no

later than March 7, 1991 and, therefore, the present application has been timely filed.

6. A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

Inventors: Raymond P. Warrell, Jr.
and Richard S. Bockman

U.S. Patent No. 4,529,593

Date of Issue: July 16, 1985

Date of Expiration: July 16, 2002.

7. A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the patent is attached as Exhibit 3.

8. A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

A certificate of correction was filed on January 22, 1986 and a copy of that certificate is attached as Exhibit 4. A maintenance fee was paid on January 26, 1989 and a copy of the receipt of the maintenance fee payment is attached as Exhibit 5.

9. A statement beginning on a new page that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent and demonstrates the manner in which each applicable patent claim reads on the approved product as a method of using or manufacturing the approved product.

U.S. Patent No. 4,259,593 claims the method of using the approved product, gallium nitrate, in claims 1, 2, 9, 11, 16, 17 and 18.

These claims read as follows:

> 1. Method effective against excessive loss of calcium from bone in a human individual requiring such treatment comprising administering to the individual an effective amount of a pharmaceutically acceptable gallium compound.
>
> 2. Method of claim 1 wherein said excess loss is due to hypercalcemia.
>
> 9. Method of claim 1 wherein said gallium compound is administered intravenously, subcutaneously or intramuscularly.
>
> 11. Method of claim 9 wherein said injection comprises amount ranging from about 10 - 400 mg/sq m/day.
>
> 16. Method of claim 1 wherein said gallium compound is selected from the group consisting of gallium nitrate, gallium citrate, gallium halide, gallium chloride, gallium carbonate, gallium acetate, gallium tartrate, gallium oxalate, gallium oxide and hydrated gallium oxide.
>
> 17. Method of claim 16 wherein said gallium compound is gallium nitrate.
>
> 18. Method of claim 2 wherein said gallium compound is gallium nitrate.

The approved product is gallium nitrate, a pharmaceutically acceptable gallium compound (claims 1, 16, 17, 18). It is

indicated for treatment of hypercalcemia (claims 2, 18), a condition symptomized by excessive loss of calcium from bone (claims 1, 16, 17, 18). The indicated dosage is an intravenous injection (claim 9) with a recommended dosage of 200 mg/sq m for 5 days (claim 11).

10. A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

(i) For a patent that claims a human drug product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) was initially submitted and the NDA number; and the date on which the NDA was approved.

The Investigational New Drug Application (IND 10123) for use of gallium nitrate in the treatment of cancer was filed with the Food and Drug Administration (FDA) by the National Cancer Institute (NCI) on October 11, 1973, and became effective on November 10, 1973. (Studies were performed under the IND by MSKCC for treatment of cancer-related hypercalcemia beginning on August 10, 1982. MSKCC subsequently licensed Lyphomed, Inc. to rely on data obtained from those studies. On November 17, 1987, NCI notified Lyphomed, Inc. that Lyphomed, Inc. had permission to cross-reference IND 10123).

The New Drug Application (NDA 19-961) was filed on March 17, 1989 by Lyphomed, Inc. for treatment of cancer-related hypercalcemia.

The New Drug Application (NDA 19-961) was approved by the FDA on January 17, 1991.

11. A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

A brief description of the activities undertaken by the "marketing applicant," i.e., Applicant's licensee, Fujisawa Pharmaceutical Company (formerly Lyphomed, Inc.), during the applicable regulatory review period is attached as Exhibit 6. Exhibit 6 contains a chronology of the major events in the testing of gallium nitrate by MSKCC and the communications between Fujisawa Pharmaceutical Company (or Lyphomed, Inc.) and FDA from October 9, 1973 to January 17, 1991.

Because Lyphomed, Inc.'s submission of its NDA relied upon the testing performed by MSKCC, Applicant claims the activities undertaken by both Lyphomed and MSKCC during the testing phase of the regulatory review period as applying to the marketing applicant.

12. A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

Applicant is of the opinion that U.S. Patent No. 4,529,593 is eligible for extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

(a) U.S. Patent No. 4,529,593 claims a method of using a product (35 U.S.C. § 156 (a)).

(b) The term of U.S. Patent No. 4,529,593 has not expired (35 U.S.C. § 156 (a)(1)).

(c) The term of U.S. Patent No. 4,529,593 has never been extended before submission of this application (35 U.S.C. § 156 (a)(2).

(d) This application is being submitted by the authorized agent of the owner of record of the patent in accordance with the requirements of 35 U.S.C. § 156 (d) and the rules of the United States Patent and Trademark Office (35 U.S.C. § 156 (a)(3)).

(e) The product, gallium nitrate, has been subjected to a regulatory review period before its commercial marketing or use (35 U.S.C. § 156 (a)(4)).

(f) The commercial marketing or use of the product after the regulatory review period will be the first permitted commercial marketing or use of the product under Section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355 (35 U.S.C. § 156 (a)(5)(A)).

(g) No other patent has been extended for the same regulatory review period for the product, gallium nitrate (35 U.S.C. § 156 (c)(4)).

The length of extension of the patent term for U.S. Patent No. 4,529,593 claimed by Applicant is 916 days. The length of the extension was determined pursuant to 37 C.F.R. § 1.775, as follows:

(a) Pursuant to 37 C.F.R. § 1.755 (c) the regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on November 10, 1973 and ended on January 17, 1991, which is the total of 6,277 days. This is the sum of the two phases described below:

(i) The "Testing Phase" under 35 U.S.C. § 156 (g)(1)(B)(i) began on November 10, 1973, and ended on March 17, 1989, which is 5,606 days; and

(ii) The "Application Phase" under 35 U.S.C. § 156(g)(1)(B)(ii) began on March 17, 1989, and ended on January 17, 1991, which is 671 days.

(b) Pursuant to 37 C.F.R. § 1.755(d), the length of the patent term extension is calculated as follows:

(1) The following number of days are to be subtracted from the regulatory review period:

(i) The number of days in the regulatory review period which were on or before the date on which the patent was issued, July 16, 1985, which is 4,266 days, and

(ii) The number of days in the regulatory review period during which Applicant did not act with due diligence, which (after the date of patent issuance) is zero (0) days,[1] and

(iii) One-half the number of days in the Testing Phase after the patent issued, which is 670 days;

(2) The remaining total of 1,341 days, when added to the original term of the patent, which expires July 16, 2002, would provide an exclusive marketing period lasting until March 18, 2006.

(3) Fourteen (14) years, when added to the date of NDA

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[1] Although IND (10123) became effective for studies of cancer treatment on November 10, 1973, it was not until 1982 that studies began on treatment for cancer-related hypercalcemia. Consequently, Applicant does not claim due diligence related to this marketing application during the period from November 10, 1973, the date of effectiveness of the NCI IND, and the commencement of the MSKCC clinical study on treatment of cancer-related hypercalcemia in July of 1982. Since that time period pre-dates issuance of the patent, it is not relevant to the computation of the regulatory review period.

approval, January 17, 1991, would result in the date January 17, 2005.

(4) The earlier date of those in paragraphs (2) and (3) above is January 17, 2005.

(5) Because the patent was issued after September 24, 1984, one must add five (5) years to the expiration date of the patent, leading to the date July 16, 2007.

(6) The earlier date of those in paragraphs (4) and (5) is January 17, 2005, and thus that is the date to which the patent term should be extended.

Therefore, Applicant is requesting an extension of the patent term of 916 days to January 17, 2005.

13. A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

In addition to the information provided above, Applicant notes that U.S. Patent No. 4,529,593, entitled "Use of Gallium Salts to Treat Disorder of Calcium Homeostasis," was filed June 10, 1984, U.S. Serial No. 622,726, and was a continuation of U.S. Serial No. 436,133, filed October 22, 1982, now abandoned.

14. The prescribed fee for receiving and acting upon the application for extension.

A check in the amount of $600.00 is enclosed with this application.

15. The name, address, and telephone number of the person to whom inquires and correspondence relating to the application for patent term extension are to be directed.

John P. White, Esq.
Cooper & Dunham
30 Rockefeller Plaza
New York, New York 10112
(212) 977-9550

16. A duplicate of the application papers, certified as such.

A certified copy is submitted herewith.

17. An oath or declaration as set forth in paragraph (b) of 37 C.F.R. § 1.740.

I, John P. White, hereby declare that:

1) I am a patent attorney authorized to practice before the United States Patent and Trademark Office (Registration No. 28,678) and have general authority from Sloan-Kettering Institute for Cancer Research, owner of U.S. Patent No. 4,529,593, to act on its behalf;

2) I have reviewed and understand the contents of this application;

3) I believe that the patent is subject to extension

pursuant to 37 C.F.R. § 1.710;

4) I believe that an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

5) I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 4,529,593.

Respectfully submitted,

SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH

Dated: March 7, 1991 By: _____

John P. White, Esq.
Registration No. 28,678
COOPER & DUNHAM
30 Rockefeller Plaza
New York, New York 10112
(212) 977-9550
Attorney for Assignee

Exhibit 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-961

JAN 17 1991

Fujisawa Pharmaceutical Company
Attention: Edward R. Gubish, Ph.D.
Senior Director, Regulatory Affair
Parkway North Center
3 Parkway North, 4th floor
Deerfield, IL 60015-2548

Dear Dr. Gubish:

Reference is made to your new drug application dated March 17, 1989, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ganite (gallium nitrate injection).

We also acknowledge receipt of your additional communications dated March 17, April 18, June 7, 15, and 21, July 7 and 19, August 1, 2, and 29, September 7 and 14, November 7 and 10, and December 19, 1989; January 29, February 8, 9, 20 (2), 22 (2), and 27, March 12, 28, and 29, April 3, 11, 17, 20, and 23, May 9, 14, and 22, June 5 and 25, and September 4, and 18, 1990; and January 8, 11, and 14, 1991.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling dated January 14, 1991. Accordingly, the application is approved, effective as of the date of this letter.

A spelling change, as agreed to by Dr. Hana Berger of Fujisawa during phone conversations with Ms. Nancy N. Clagett of this Division on January 15 and 17, 1991, should be made in the package insert, PRECAUTIONS, Laboratory Tests, and ADVERSE REACTIONS, Metabolic, subsections. The word "phosphorous" should be changed to "phosphorus." In addition, in the ADVERSE REACTIONS section, Miscellaneous subsection, first sentence, the words "have been" should be deleted.

Please submit twelve (12) copies of the revised final printed labeling (FPL) identical to the draft labeling, but including the changes noted above, as soon as available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 19-961." Approval of the submission by FDA is not required before the labeling is used. If the flip-off cap contains wording on the use of the product (e.g., "Dilute before use"), it is considered part of the labeling of the product and specimens should be submitted along with the vial label, carton, and package insert. Marketing of the product with FPL that is not identical to the draft labeling, as amended above, may render the product misbranded and an unapproved new drug. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of that labeling may be required.

We reserve comment as to the adequacy of the methods validation package for bulk gallium nitrate until the results of our laboratory tests on the samples submitted are available and have been evaluated. If these results indicate some modifications of the proposed methods are necessary before they can be accepted, or additional samples are required, your coorperation, as well as that of the bulk supplier, will be expected in finalizing the procedures.

In addition, we request the inclusion of a resolution test in document #RD8-TR-042 of the Fujisawa methods validation package for the determination of sodium citrate dihydrate, specifically indicating the acceptable resolution between nitrate and citrate for the reliable quantitation of citrate.

In your May 9, 1990, and January 11, 1991, submissions, you committed to performing the following Phase 4 pharmacokinetics studies and providing results of ongoing comparative studies:

1. A pharmacokinetics study in hypercalcemic patients with varying degrees of renal dysfunction in three groups of eight patient as follows:

Creatinine Clearance	Dose/Schedule
15-30 mL/min	100 mg/m^2/day continuous IV infusion for 5 days
30-60 mL/min	200 mg/m^2/day continuous IV infusion for 5 days
>60 mL/min	200 mg/m^2/day continuous IV infusion for 5 days

2. A pharmacokinetics study at different doses and schedules in three groups of five patients as follows:

400 mg/m^2/day as a continuous IV infusion for 2 days
300 mg/m^2/day as a continuous IV infusion for 3 days
100 mg/m^2/day as a 4 hour infusion daily for 5 days

Subsequent to completing these studies, you have agreed to meet with the Agency tc discuss whether any of the doses and schedules should be studied for safety and efficacy in comparison to the approved 200 mg/m^2/day IV infusion for 5 days. Also to be discussed at the completion of these studies will be safety and efficacy in patients who have relapsed or who require a second course of treatment.

3. Results of the comparative study with etidronate by March 1, 1991.

4. Results of the comparative study with pamidronate at the completion of the study.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

(3)

United States Patent [19]

Warrell, Jr. et al.

[11] Patent Number: 4,529,593

[45] Date of Patent: Jul. 16, 1985

[54] USE OF GALLIUM SALTS TO TREAT DISORDERS OF CALCIUM HOMEOSTASIS

[75] Inventors: Raymond P. Warrell, Jr.; Richard S. Bockman, both of New York, N.Y.

[73] Assignee: Sloan-Kettering Institute for Cancer Research, New York, N.Y.

[21] Appl. No.: 622,726

[22] Filed: Jun. 20, 1984

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 436,133, Oct. 22, 1982, abandoned.

[51] Int. Cl.³ A61K 33/00

[52] U.S. Cl. 424/127

[58] Field of Search 424/127

[56] References Cited

PUBLICATIONS

Warrell et al., J. Clin. Invest., vol 73, May 1984, pp. 1487-1490.

Merck Index, 9th (1976), pp. 560-566.

Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Felfe & Lynch

[57] ABSTRACT

The present invention comprises a method of preventing or treating a disorder associated with accelerated loss of calcium from bone in a human individual comprising administering to the individual a pharmaceutically acceptable gallium compound. Of especial importance among the disorders which may be thus prevented or treated are hypercalcemia, accelerated bone loss associated with osteopenia, osteoporosis, bone metastasis due to malignant tumors, and hyperparathyroidism. In the method of the present invention gallium compounds may be administered by any and all routes.

Although all biocompatible, soluble compounds of gallium may be used in the present invention, gallium nitrate is preferred, most preferably in a pharmaceutically acceptable carrier.

24 Claims, No Drawings

USE OF GALLIUM SALTS TO TREAT DISORDERS OF CALCIUM HOMEOSTASIS

This application is a continuation-in-part of application Ser. No. 130,133, now abandoned.

This invention concerns the use of gallium compounds to treat disorders associated with calcium loss from bone.

BACKGROUND

Loss of bone mass (osteopenia or osteoporosis) and accelerated loss of calcium from bone are major causes of medical illness. Increased bone resorption is commonly associated with many different diseases. These problems affect millions of persons in the U.S. alone. Examples of disorders due to increased bone resorption include: (a) Osteoporosis (loss of bone mass)—a major source of morbidity producing hip and vertebral fractures in elderly, post-menopausal women; (b) hypercalcemia (increased blood calcium concentrations)—a problem which occurs frequently in patients with hyperparathyroidism or cancer which can produce kidney failure, coma and death if not treated; (c) bone metastasis (spread of cancer cells into bone). In the absence of effective antitumor therapy (and this problem frequently afflicts persons who have proved resistant to anticancer therapy), cancer cells progressively erode the bone causing fractures and extreme pain. Clearly, a drug which could directly strengthen bone tissue and decrease bone resorption would be highly desirable.

A variety of treatments have been utilized to treat these various disorders (e.g. fluorides and estrogens for osteoporosis; intravenous fluids, diuretics, phosphates, and mithramycin for hypercalcemia; radiation treatments for bone metastases if the disease is not extensive). Each of these treatments suffers from certain disadvantages such as excessive toxicity, production of disordered bone growth, or weak activity.

Accordingly, a search has been undertaken to discover agents which inhibit calcium resorption from bone.

Gallium is a metal which belongs to the Group IIIa elements of the periodic table. By mechanisms which are still uncertain, radioactive gallium salts are known to accumulate in certain tumors (Dudley H. C. et al. Radiology, 50: 571, (1950). 67-Gallium citrate is currently used for diagnostic purposes in patients with bone infections and malignant diseases (McCaffrey J. A. et al. AM J Med 60: 523, 1976; Hoffer, P. J Nuc Med 21: 394, (1980)). In 1952, King et al (Arch. Int. Med. 90:785 (1952)) first showed that injections of highly radioactive gallium caused tumor regression in cancer patients. Non-radioactive salts of gallium and other Group IIIa metals were first evaluated for their anticancer activity in 1971 (Hart, M. M., Adamson R. H. et al. Proc Nat Acad Sci (USA) 68:1623, 1971; Hart, M. M., Smith C. F., et al. J Nat Cancer Inst 47:1121, (1971)). Gallium was found to be the most potent and least toxic element for reducing the size of animal tumors. The anionic component (whether the salt was a nitrate or a chloride) made no significant difference with respect to the direct anticancer action (Adamson, R. H. et al. Cancer Chemother Rep 59:599, (1975)). After completing preclinical toxicologic studies, gallium nitrate entered into clinical trials as a cytotoxic anticancer agent in 1976. U.S. Pat. No. 4,303,636 discloses a method of cancer treatment which uses radioactive 67-gallium, as a cytotoxic agent.

It is the use of gallium as an inhibitor of calcium resorption from bone that is the subject of the present invention.

SUMMARY OF THE INVENTION

It is a principal object of the present invention to provide a method for regulating resorption of calcium from bone.

It is another principal object of the present invention to provide a method of treating disorders associated with excessive loss of calcium from bone.

It is another object of the present invention to provide a method of preventing and treating hypercalcemia associated with cancer or hyperparathyroidism, two of the more common causes.

It is an important object of the present invention to provide a method of treating or preventing osteopenia or osteoporosis due to calcium resorption from bone. Factors which may be associated with osteopenia or osteoporosis include aging (especially in women), surgical castration, immobilization, and other causes.

It is a further object of the present invention to provide a method for the treatment or prevention of accelerated calcium loss from bone and bone destruction caused by direct invasion of bone by malignant tumors or by the secretion of bone-resorbing factors by cancer cells.

It is a further object of the present invention to provide a method for the treatment or prevention of accelerated calcium loss from bone, osteoporosis, osteopenia, and other diseases associated with increased bone resorption in animals.

It is further object of the present invention to provide a method of inhibiting release of calcium from cultured bones.

It is a further object of the present invention to provide a method of administering gallium salts in in amounts effective in treatment of both acute and chronic hypercalcemia.

It is a special object of the present invention to provide a method for treatment or prevention of accelerated calcium loss from bone due to periodontal disease.

In accordance with these objectives, the present invention comprises the pharmacologic use in humans and animals of any and all pharmaceutically acceptable non-radioactive gallium salts in non-nephrotoxic amounts to inhibit resorption of calcium from bone in patients with hypercalcemia, bone fragility or other disorders associated with abnormally increased calcium resorption.

A method of preventing or treating a disorder associated with extensive loss of calcium from bone in humans comprising administering to the individual a pharmaceutically acceptable gallium compound is disclosed. Of especial importance among the disorders which may be thus prevented or treated are hypercalcemia, osteopenia, osteoporosis, bone destruction due to metastasis from malignant tumors, and hyperparathyroidism. In the method of the present invention gallium compounds are preferably administered by intravenous subcutaneous or intramuscular injection including continuous infusion preferably in amounts from 10–400 mg/sqm/day whereby plasma gallium concentrations are maintained at about 0.9-2.0 ug/ml. The gallium compounds of the present invention also may be administered orally, sub-lingually, per rectum or transder-

mally, preferably in doses of 0.5 to 20 grams per day. Although all biocompatible, soluble compounds of gallium may be used in the present invention, gallium nitrate is preferred, most preferably in a pharmaceutically acceptable carrier. Preferred carriers are suitably buffered aqueous solutions, for example phosphate buffered saline or citrate buffers.

DETAILED DESCRIPTION

The present invention comprises a method of administering gallium salts, preferably gallium nitrate, along with a pharmaceutically acceptable carrier in non-nephrotoxic amounts to patients with hypercalcemia due to resorption of calcium from bone. Gallium salts which may be employed are those which are physiologically acceptable including nitrate, citrate, halide, preferably chloride, carbonate, acetate, tartrate, oxalate, oxide or hydrated oxide. It is to be understood that the active therapeutic agent is the gallium ion and, that therefore the choice of an ion may be determined by such factors as commercial accessibility, solubility characteristics, and mode of administration.

The gallium salt may be administered orally, sub-lingually, intramuscularly, subcutaneously, intravenously, transdermally or per rectum. The anticalcium effect of gallium salts is schedule-related (i.e. prolonged exposure to lower concentrations produces greater inhibition of bone resorption than short treatment with high doses). By example, in the preferred embodiment of the present invention, gallium nitrate for the treatment of cancer-related hypercalcemia is administered by continuous infusion for several days, followed by chronic treatment to prevent recurrence.

In the treatment of loss of calcium from bone due to periodontal disease the gallium compound may administered topically in an intra-oral formulation comprising, for example, a highly concentrated rinse, gel, or other pharmaceutically acceptable carrier for the local treatment of periodontal disease.

Pre-clinical Studies with Gallium Nitrate

A. GALLIUM EFFECTS ON WHOLE BONES IN VITRO.

Summary: Calcium releases from rat bones can be stimulated by various natural substances, including parathyroid hormone (PTH) and also by a factor derived from cancer cells which is similar to osteoclast activating factor ("OAF", a lymphokine). Gallium nitrate inhibits calcium release induced by both of these substances. The degree of inhibition was both time- and dose-dependent.

Experimental Data

The effects of gallium nitrate on bone resorption in vitro were studied using explants of fetal rat bones (Bockman, R. S. and Repo, M. A., J Exp Med 154:529, 1981). Pregnant rats were injected with 0.2-0.4 mCi of 45-CaC12 on the 18th day of gestation. After 2 days of bone mineralization in utero, the radii and ulnae of fetal rats were explanted and placed on stainless steel rafts in BGJ media. Calcium releases from bone was stimulated by the addition of bovine PTH (2.0 microM, final concentration) or lymphokine (OAF) preparation (10% of final volume). Gallium nitrate was added to the culture media at final concentration of 1, 5 and 10 mcg/ml simultaneously with—and 18 or 48 hours prior to—the addition of the bone-resorbing factors. After 48 hours of exposure to lymphokine or PTH, calcium release was determined by counting the supernatant media in a liquid scintillation counter. Data were expressed as the ratio of calcium release in counts per minute (cpm) of the experimental bone (treated or untreated with gallium nitrate and a resorbing factor) to cpm release by a paired control bone (treated or untreated with gallium nitrate) {cpm experimental/cpm control = E/C} Forty-nine bones were used to establish control values; 4–22 bones were used to obtain each of the experimental points.

The inhibitory effect of gallium nitrate upon bone resorption was found to be time-dependent. Addition of gallium nitrate (10 mcg/ml) simultaneously with (time 0), or 18 hrs preceeding the addition of PTH or lymphokine, decreased 45-Ca++ release relative to control bones incubated with lymphokine only, but the reduction was not statistically significant. However pre-incubation of bones for 48 hours preceeding the addition of lymphokine caused a highly significant reduction in lymphokine-induced 45-Ca++ release.

The inhibitory effects of gallium on PTH- or lymphokine-stimulated bone resorption was also found to be dose-dependent. After 48 hrs of preincubation, 1 mcg/ml of gallium nitrate caused no significant change in 45-Ca++ release after stimulation by PTH or lymphokine. However, significant and dose-related reductions in 45-Ca++ release were observed using concentrations of 5 and 10 mcg/ml of gallium nitrate, P less than 0.025.

B. EFFECTS OF GALLIUM UPON BONE CELLS.

Summary: Prior work (Warrell, R. P. Jr, Coonley, C. J. et al, Cancer 51:1982, (1983). Adamson, R. H. et al, Cancer Chemother Rep 59:599, (1975)) has established that gallium has modest anticancer activity against certain animal and human tumors. Other anticancer drugs, specifically a drug called mithramycin, can also reduce blood calcium levels. However, mithramycin causes this effect by directly killing bone cells (Minkin, C. Calcif Tissue Int 13:249, 1973). Therefore, the anti-calcium effect could be non-specifically related to lethal effects on both normal and cancerous cells.

Several experiments were performed to determine whether gallium was toxic to bone cells, and thus whether its anti-calcium effect was non-specifically related to lethal cellular effects. The results showed: (1) that pharmacologic concentrations of gallium do not cause lethal toxicity to bone cells; and (2) that the mechanism whereby gallium inhibits bone resorption is clearly different from mithramycin.

Experimental Data: Mithramycin causes considerable loss of bone cells (particularly osteoclasts) number after comparatively brief exposure (Minkin, C. Calcif Tissue Int 13:249, 1973; R. S. Bockman, unpublished observations). Samples of cultured rat bones used in experiments previously described herein were fixed, decalcified and stained with hematoxylin and eosin. Histologic sections were examined by light microscopy. By comparison with mithramycin-treated bones, bones exposed to pharmacologic concentrations of gallium for 72 hrs showed normal cellular components. Moreover, no differences in bone cell morphology were noted relative to untreated control bones. Specifically, both osteoclast number and size were similar in treated and untreated bones.

Furthermore, gallium treatment alone (i.e., without added PTH or lymphokine as in the preceding experiments) did not have any effect on 45-Ca- - release compared to control bones not exposed to gallium

These data also indicate that the drug caused no cytotoxic effect on bone.

It has previously been shown that normal metabolism of fetal rat bones is associated with prostaglandin (PGE2) production in the basal state. In addition, PGE2 production can be markedly stimulated by lymphokine preparations that contain OAF (Bockman, R. S. and Repo, M. A., J Exp Med 154:529, 1981). When PGE2 release from explanted bones that had been exposed to gallium nitrate (10 mcg/ml) for 24–48 h was examined, no change in PGE2 over control (non-treated) bones was observed. No increase in bone calcium release (measured as 45-Ca^{++}) was noted during the 48 h incubation with gallium nitrate compared with controls. Exposure of gallium treated bones to lymphokine, but not PTH caused a significant increase in PGE2 release as previously reported (Bockman, R. S. and Repo, M. A., J Exp Med 154:529, 1981). Prior exposure (48 h preincubation) to 1.5 and 10 mcg/ml gallium nitrate caused a dose dependent decrease in 45-Ca^{++} release but no significant change in PGE2 release was observed. Table 1.

TABLE 1

	45-Ca^{++} release expt'l / 45-Ca^{++} release control		PGE2 (ng/bone)	
Gallium mcg/ml	PTH	Lymph	PTH	Lymph
0	1.21 ± 0.15	1.59 ± 1	1.4	17.1
1	1.24	1.54 ± 16	2.2	17.4
5	1.08	1.21 ± 04	1.3	16.7
10	0.99	1.23 ± 04	3.9	15.1
Control	1.00 ± .06	1.00 ± 06	1.2	2.0

Thus, these results (which demonstrate both intact metabolic function and normal histologic appearance) indicate that the anti-calcium activity of gallium is not mediated through a cytotoxic effect.

C. GALLIUM INCORPORATION INTO BONE MINERAL.

It was found that gallium is directly incorporated into bone material.

In rats treated with gallium nitrate, gallium was incorporated into the bone metaphysis where more active bone mineral turnover was occurring and into the metabolically more active crystalline pool (less calcified matrix). The most striking finding by X-ray diffraction was a marked increase in crystal size in the metaphyseal-derived particles from the gallium treated animals as compared to controls. Conceivably, gallium promotes or stabilizes crystal structure to produce matrix with more crystalline hydroxyapatite, or the drug promotes growth rather than dissolution of smaller crystallites.

D. ANTI-RESORPTIVE EFFECTS OF GALLIUM ON DEVITALIZED BONE

Devitalized bone particles (i.e. bones containing only mineral and matrix without any cellular component) were studied. Such particles from rats tested with gallium nitrate were significantly less susceptible to resorption than controls. This experiment shows that the anti-resorptive effects of gallium are not due to cytotoxic action upon bone cells.

E. ORAL ABSORPTION OF GALLIUM NITRATE

Summary: As previously noted, the intravenous route has been employed for clinical use. The method of subcutaneous and intraperitoneal injections have been employed in rats.

To evaluate the oral absorption and excretion of gallium nitrate, a concentrated solution of the drug was administered to a dog by oral gavage (total dose = 1200 mg). Sequential plasma samples and the next 24 hour urinary volume were collected and assayed for gallium concentration by a flameless atomic absorption spectrophotometer (Kelsen, D. P. et al, Cancer 46:2009, 1980).

Importantly, the dog sustained no toxic reaction from this treatment whatsoever. The subsequent 24 hour urine volume was 183 ml and it contained a total amount of 1.13 mg of elemental gallium. Assuming similar patterns of excretion in humans and dogs, it is estimated that approximately 0.5–2% of an orally administered dose is absorbed and excreted into the urine. Plasma gallium levels after oral gavage of dog are shown in Table 5.

Table 5: Plasma gallium concentrations in the dog after administration of a single oral dose.

Time hrs	Gallium Concentration (mcg/ml)
0	0
0.25	0.5
0.5	1.25
1	1.37
2	2.75
4	2.0
24	0.75

Previous studies (Kelson, D. P. et al, Cancer 46:2009, 1980) have demonstrated that intravenous infusions used in the clinical studies at the dose employed in the clinical studies described below achieve steady-state plasma gallium concentrations which range from 0.9–2.0 mcg/ml. The dog experiment shows that these levels which comprise effective treatment for cancer-related hypercalcemia associated with increased bone resorption are achieved by the oral route. In the preferred embodiment of this invention, administration of gallium 1–4 times per day would be expected to maintain low-level plasma gallium concentrations which are therapeutic for disorders of calcium homeostasis. Extrapolating from the dog data, it is estimated that 0.5–20 gms of gallium nitrate administered orally to a 70 kg human will achieve effective plasma levels. A broader range of gallium plasma levels which are not nephrotoxic is also possible.

CLINICAL STUDIES

F. METABOLIC STUDY OF PATIENTS RECEIVING GALLIUM NITRATE

Summary: Contrary to a previous report in the medical literature (Krakoff, I. H. et al, Cancer 44:1722, 1979), patients who received gallium nitrate in the present studies showed decreased urinary calcium excretion and remained in positive calcium balance while receiving the drug (i.e. retaining more calcium than they excreted). As with most anticancer drugs, gallium can potentially cause serious toxicity. The most serious side-effect being kidney damage. However, studies using sensitive analytical techniques show that nephrotoxicity is generally reversible and that it is not cumulative (Leyland-Jones, B. R. et al, Cancer Treat Rep 67:941, 1983). It has also been found that intermittent high-dose infusions can be administered for 22 months without serious toxicity. Furthermore, the anti bone-resorptive effects of gallium nitrate are achieved

with less than 25–50% of the anticancer dose. Thus the method should retain safety and efficacy for prolonged periods of time.

Experimental Results: Studies of calcium homeostasis require an assessment of multiple factors including dietary intake, excretion of calcium into urine and stool, and analysis of calcium mobilization from body stores (chiefly bone). Four patients who participated in a careful study of the effects of gallium nitrate upon calcium metabolism were thus assessed. Patients were hospitalized and received a diet of defined calcium, sodium, and fluid intake. Measurements of calcium excretion into urine and stool (along with multiple other laboratory tests) were made daily during a 6-day baseline period and during a subsequent treatment period using gallium nitrate. The drug was administered as a continuous infusion at a dose of 300 mg/sq m/day for durations ranging from 4–7 days. Despite the finding that the total serum calcium concentration was reduced by the gallium infusion, we found no significant increase in calcium excretion during the infusion relative to the baseline observation period. These data suggested that gallium nitrate might exert its hypocalcemic effect by directly affecting calcium resorption from bone (Warrell, R. P. Jr, Bockman, R. S. et al, Clin Res 31:511A, (1983)).

G. TREATMENT OF CANCER-RELATED HYPERCALCEMIA WITH GALLIUM NITRATE

Summary: In the initial study, gallium nitrate was used for the treatment of 10 patients with cancer-related hypercalcemia. The daily dose of drug was 200 mg/sq m administered as a continuous infusion for durations ranging from 5–7 days. The diagnoses of this patient population and the change in total serum calcium concentration in response to this therapy are presented in Table 4a. Note that all patients responded to this treatment by a reduction in serum calcium concentration to normal (and frequently sub-normal) values.

With the single exception of Patient 5 (Table 4a), the hypocalcemic effect was not associated with any anticancer effect. Patient 5 demonstrated a transient decrease in the size of a lymphomatous mass followed shortly thereafter by progression of her disease and death. The subsequent increase of her disease was not accompanied by an increase in serum calcium which indicates a persistent control of the metabolic problem despite lack of control of the underlying cancer. All other patients who received the drug manifested progressive cancer despite control of the hypercalcemia. This finding indicates that the hypocalcemic effect is not produced by a direct cytotoxic effect of gallium nitrate upon tumor cells. In a subsequent study, we further reduced the daily dose of gallium nitrate to 100 mg/sq m administered for 5 days. At a lower dose, 5 of 8 patients w[illegible] normalized (Table 4b). These preliminary clinical results reflect our preclinical studies previously detailed, namely that there exists a distinct dose-response relation to the anticalcium effect (Warrell, R. P. Jr, Bockman, R. S. et al, J. Clin. Invest. 73:1487 (1984)).

TABLE 4a

Response of patients with cancer-related hypercalcemia to continuous infusion of gallium nitrate (dose = 200 mg/sq m/d × 5–7 d).

Patient	Cancer Diagnosis	Total Serum Calcium* Pre-Treatment	Total Serum Calcium* Post-Treatment
1	Breast	13.8	8.9
2	Breast	15.2	8.5
3	Lymphoma	15.6	6.6
4	Head & Neck	12.3	8.5
5	Breast	14.4	7.7
6	Lymphoma	15.6	8.6
7	Lung	12.5	7.0
8	Penis	12.3	9.3
9	Head & Neck	13.5	7.8
10	Lung	13.7	9.3

TABLE 4b

Response of patients with cancer-related hypercalcemia to gallium nitrate (dose = 100 mg/sq m/d × 5 d).

Patient	Diagnosis	Pre-Treatment	Post-Treatment
1	Breast	13.9	11.3
2	Anus	12.7	6.3
3	Kidney	14.3	12.0
4	Breast	14.5	8.7
5	Pancreas	14.6	10.0
6	Myeloma	15.0	13.7
7	Lung	13.0	10.8
8	Breast	17.0	9.0

(*Serum concentration expressed in mg/dl (normal range, 9.0–10.5 mg/dl).

G. GALLIUM NITRATE DECREASES BONE TURNOVER IN PATIENTS WITH CANCER METASTATIS TO BONE

Summary: Patients with bone metastasis suffer progressive erosion of bone which causes pain, immobilization and fractures. Clinically, bone metastases are evaluated by sequential x-rays over a period of months to years. Other measures have recently been employed to measure bone turnover in patients with both cancer and non-cancerous bone resorption. In general, increased bone turnover is associated with increased loss of calcium into the urine and with increased excretion of hydroxyproline (a component of hydroxyapatite). Measurements of these parameters have been used to assess whether a new drug affects bone resorption (Siris, E. S. et al, New Engl J Med 302:310, 1980). We recently measured these parameters in a patient with multiple myeloma and extensive bone destruction who received gallium nitrate (200 mg/sq m/d × 7 d by infusion).

As shown in Table 6, a marked decrease in the amount of calcium and hydroxyproline excretion was observed, indicating that the drug was effective in reducing bone resorption in this patient. The biochemical improvement was also accompanied by a substantial decrease in bone pain and a reduced requirement for narcotics. There was no effect upon the underlying disease and the patient has since received other chemotherapy for her myeloma.

TABLE 6

Gallium effects on bone turnover

Days in Treatment	Urine Volume (mL/24 h)	Calcium (mg/24 h)	Phosphorus (mg/24 h)	OHP — Proline (mg/24 h)
1 Pre-[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
1	[illegible]	[illegible]	[illegible]	[illegible]

TABLE 6-continued

Gallium effects on bone turnover.

Days in Treatment	Urine Volume (ml/24 h)	Calcium (mg/24 h)	Phosphorus (mg/24 h)	OH—Proline (mg/24 h)
4	3620	239	607	23.9
8	3225	97	419	19.0

What is claimed:

1. Method effective against excessive loss of calcium from bone in a human individual requiring such treatment comprising administering to the individual an effective amount of a pharmaceutically acceptable gallium compound.

2. Method of claim 1 wherein said excess loss is due to hypercalcemia.

3. Method of claim 1 wherein said excess loss is due to osteopenia or osteoporosis.

4. Method of claim 1 wherein said excess loss is due to bone metastasis from malignant tumors.

5. Method of claim 1 wherein said excess loss is due to hyperparathyroidism.

6. Method of claim 1 wherein said excess loss is due to periodontal disease and said gallium compound is administered intra-orally in a topical formulation comprising a concentrated rinse, gel or other pharmaceutically acceptable carrier.

7. Method effective against excessive loss of calcium from bone in animals requiring such treatment comprising the administering to said animals of an effective amount of a pharmaceutically acceptable gallium compound.

8. Method of inhibiting release of calcium from bone explants comprising contacting said explants with a gallium compound.

9. Method of claim 1 wherein said gallium compound is administered intravenously, subcutaneously or intramuscularly.

10. Method of claim 3 wherein intravenous injection comprises continuous infusion.

11. Method of claim 9 wherein said injection comprises amount ranging from about 10–400 mg/sq m/day.

12. Method of claim 1 wherein the amount of said administered gallium compound is sufficient to maintain a steady state plasma gallium concentration ranging from about 0.1–5.0 ug/ml.

13. Method claim 12 wherein the amount of said administered gallium compound is sufficient to maintain a steady state plasma gallium concentration ranging from about 0.9–2.0 ug/ml.

14. Method of claim 1 wherein said gallium compound is administered orally, sub-lingually, per rectum or transdermally.

15. Method of claim 14 wherein the amount of administered gallium compound comprises amounts from about 0.5–20 grams/day.

16. Method of claim 1 wherein said gallium compound is selected from the group consisting of gallium nitrate, gallium citrate, gallium halide, gallium chloride, gallium carbonate, gallium acetate, gallium tartrate, gallium oxalate, gallium oxide and hydrated gallium oxide.

17. Method of claim 16 wherein said gallium compound is gallium nitrate.

18. Method of claim 2 wherein said gallium compound is gallium nitrate.

19. Method of claim 3 wherein said gallium compound is gallium nitrate.

20. Method of claim 4 wherein said gallium compound is gallium nitrate.

21. Method of claim 5 wherein said gallium compound is gallium nitrate.

22. Method of claim 6 wherein said gallium compound is gallium nitrate.

23. Method effective against bone pain due to excessive loss of calcium from bone in a human individual requiring such treatment comprising administering to the individual an effective amount of pharmaceutically acceptable gallium compound.

24. Method effective against bone fractures due to excessive loss of calcium from bone in human a individual requiring such treatment comprising administering to the individual an effective amount of a pharmaceutically acceptable gallium compound.

* * * * *

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,529,593

DATED : July 16, 1985

INVENTOR(S) : Raymond P. Warrell, Jr. et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 2, line 39: delete second "in";

line 62: after "intravenous" insert --,--.

Column 3, line 44: change "**releases**" to --release--;

line 60: change "releases" to --release--.

Column 6, line 17: change "5" to --2--'

line 18: change "5" to --2--;

line 61: change "being" to --is--.

Column 7, line 41: change "4a" to --3a--;

line 44: change "4a" to --3a--;

line 62: change "4b" to --3b--.

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CERTIFICATE OF CORRECTION

PATENT NO. : 4,529,593

DATED : July 16, 1985

INVENTOR(S) : Raymond P. Warrell, Jr. et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8, change "TABLE 4a" to --TABLE 3a--, and "TABLE 4b" to --TABLE 3b--

line 32: change "G" to --H--;

line 33: change "METASTATIS" to --METASTASIS--;

line 51: change "6" to --4--;

line 61: change "6" to --4--.

Column 9, line 1: change "6" to --4--.

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in the following listed application(s) or patent(s) for which the Issue Fee has been paid.

PATENT NUMBER (if known)	SERIAL NUMBER	PATENT DATE (if known)	U.S. FILING DATE
4,529,593	622,726	July 16, 1985	June 20, 1984

Typed name of person signing John P. White

Signed _____

(check one) ☐ Owner of record

☒ Owner's attorney or agent of record 28,678
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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

6

Gallium Nitrate - Major Activities

10/9/73	(submitted)	
10/11/73	(received)	IND #10123 filed by NCI for citrated solution of gallium nitrate (basis for antihypercalcemia studies 82-100C and 85-30A by MSKCC
11/10/73		IND #10123 became effective
7/10/82		First patient in MSKCC clinical study 82-100C on use of gallium nitrate for the acute treatment of cancer-related hypercalcemia
6/11/85		Last patient observation in study 82-100C
8/5/85		First patient in MSKCC clinical study 85-30A on efficacy of gallium nitrate in comparison with calcitonin for acute treatment of cancer-related hypercalcemia
5/20/87		Last patient observation in study 85-30A
6/3/87		First patient in MSKCC clinical study on gallium nitrate in comparison with etidronate for acute treatment of cancer-related hypercalcemia
7/1/87		License agreement between Lyphomed and MSKCC
9/17/87		Notification by NCI to FDA that Lyphomed (now Fujisawa) may cross reference NCI IND #10123
10/7/87		Lyphomed application for designation as an orphan drug
10/20/87		Meeting between Lyphomed, NCI, MSKCC and FDA to discuss clinical studies
9/15/88		Gallium nitrate Pre-NDA package
11/2/88		Meeting at FDA during which Lyphomed presented ADR summary to FDA

In re: U.S. Patent No. 4,529,593

11/22/88		Telephone call between Lyphomed and FDA about the studies that should be included in the NDA and letter from Lyphomed to FDA confirming the substance of the call with FDA
12/5/88		FDA designation of gallium nitrate as an orphan drug
1/4/89		Mutagenicity test completed by Hazelton Laboratories, Inc.
1/27/89		Cytogenicity test completed by Hazelton Laboratories, Inc.
3/17/89		Lyphomed Submission of NDA #19-961
5/10/89 5/11/89	(submitted) (received)	IND #33155 filed by Lyphomed for gallium nitrate by subcutaneous route for treatment of cancer-related hypercalcemia
5/17/89		Telephone call from FDA to Lyphomed notifying Lyphomed that NDA preliminary review had been completed
5/20/89		Official filing date for NDA #19-961
6/7/89		Letter from Lyphomed to FDA requesting meeting to discuss medical review of NDA #19-961
6/12/89		Lyphomed submission of desk copy of clinical studies 82-100C and 85-30A
6/19/89		Telephone call to Lyphomed from FDA requesting further information on clinical studies 82-100C and 85-30A
6/21/89		Telephone calls between Lyphomed and FDA about corrosivity
6/21/89		Letter from Lyphomed to FDA requesting meeting to discuss medical review of NDA #19-961

In re: U.S. Patent No. 4,529,593

6/29/89		Telephone call between Lyphomed and FDA to schedule meeting to discuss medical review
6/29/89		Telephone call to Lyphomed from FDA requesting that finished product samples be sent to FDA laboratories
6/30/89		Lyphomed submission of clinical investigator Form 1573 for Dr. Raymond Warrell, Jr. of MSKCC to FDA
7/6/89		Letter from FDA to Lyphomed concerning deficiencies in chemistry section of NDA #19-961
7/7/89		Lyphomed submission of light stability report to FDA
7/10/89		Lyphomed submission of product samples to FDA laboratories
7/12/89		Meeting at FDA concerning medical review of NDA #19-961
7/19/89		Letter from Lyphomed to FDA concerning outcome of 7/12/89 meeting
7/22/89		Telephone call from Lyphomed to FDA for clarification of letter from FDA of 7/6/89
8/1/89		Lyphomed submission of chemistry/manufacturing/control amendment to NDA #19-961 to FDA
8/9/89 8/10/89	(submitted) (received)	IND #33155 Amendment #1 - protocol for ongoing study GN001 for gallium nitrate maintenance in cancer-related hypercalcemia
8/11/89		FDA telephone request to Lyphomed for biostatistics information
8/14/89		Telephone call between Lyphomed and FDA to discuss agenda for advisory committee meeting

8/15/89		Telephone call from Lyphomed to FDA concerning study on gallium nitrate vs. etidronate in acute treatment of hypercalcemia
8/18/89		Lyphomed submission of interim report on ongoing randomized double-blind, multicenter study on gallium nitrate vs. etidronate in acute treatment of hypercalcaemia
8/24/89		FDA telephone request to Lyphomed for additional information on serum calcium levels from clinical study 82-100C
8/29/89		Lyphomed submission of agenda for advisory committe meeting to FDA
9/89		Gallium nitrate Annual Report submitted to FDA by NCI
9/12/89		Telephone call between Lyphomed and FDA about clinical data
9/14/89		Lyphomed submission of clinical data on serum calcium levels to FDA
9/15/89		Lyphomed submission of material for advisory committee to FDA
10/8/89		Lyphomed submission of interim study report on etidronate study to FDA
10/13/89		Lyphomed submission of product labeling to FDA
10/13/89		Presentation by Dr. Raymond Warrell, Jr. of MSKCC to FDA Endocrinologic and Metabolic Drug Advisory Committee Meeting
11/10/89		Lyphomed submission of product labeling to FDA
11/21/89		Telephone call between Lyphomed and FDA concerning labeling
2/8/90		Lyphomed submission of revised product labeling to FDA
3/2/90	(submitted)	IND #33155 Amendment #6 -

3/7/90	(received)	revised protocol for gallium nitrate in treatment of bone metastases relating to breast cancer
4/11/90		Lyphomed submission of revised product labeling to FDA
4/17/90		Lyphomed submission of revised product labeling to FDA
4/20/90		Notification to FDA of name change from Lyphomed, Inc. to Fujisawa Pharmaceutical Company
4/23/90		Submission of Safety Update for NDA #19-961 to FDA.
5/22/90		Transfer of NDA 19-961 ownership to Fujisawa Pharmaceutical Company
6/27 & 29/90		Telephone call to FDA by D. Baker in regard to Grand Island manufacturing facility
9/4/90		Stability data for 24 months submitted to FDA
9/18/90		Promotional literature reviewed by FDA and comments received
10/4/90		Telephone call with FDA regarding concerns with the Phase IV commitments
10/9/90		Chronology of the Phase IV commitments, meeting and agreements submitted to FDA
11/28/90		Requests by FDA for product - specific inspection of the manufacturing facility
11/29/90		Telephone call to FDA regarding Grand Island manufacturing facility being cleared
12/12/90		Inspection of Grand Island manufacturing facility initiated
12/28/90		Grand Island inspection continued until December 31, 1990
12/31/90		Telephone calls with FDA regarding its comments respecting product

	labeling and review of data in view of requested labeling changes
1/2/91	FDA requests Biometrics Department input on the product labeling. Telephone conferences among Fujisawa and FDA Biometrics Division and Metabolism Division
1/3/91	Submission of revised product labeling to FDA
1/10/91	Meeting between Fujisawa personnel and the FDA Biometrics and Metabolism Divisions respecting product labeling
1/11/91	Revised labeling submitted to the FDA
1/16/91	Final meeting at FDA
1/17/91	Approval letter issued